# Pharmacokinetics Of Dexamethasone In Pigs

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## Introduction

Dexamethasone (DEX), a synthetic long-acting corticosteroid, is extensively used in veterinary practice as it possesses major anti-inflammatory effects. Moreover, in pigs, immunomodulatory properties of this drug have been reported. In further research, DEX will be used in a porcine lipopolysaccharide (LPS) inflammation model as a positive control, however, exact data in literature on the disposition of DEX in pigs are lacking.
The aim of this study was therefore to determine the pharmacokinetic (PK) parameters i.e. area under the curve, AUC; absorption and elimination rate constant, $k_{abs}$ and $k_{el}$; half-life of absorption and elimination, $T_{1/2abs}$ and $T_{1/2el}$; volume of distribution, $V_d$; clearance, Cl; maximum plasma concentration at 0 h, $C_0$; maximum plasma concentration, $C_{max}$; time to $C_{max}$, $T_{max}$ and absolute bioavailability, F of DEX in pigs.

## Results

The semi-logarithmic plots of the plasma concentration-time curves after IV and IM administration are depicted in Fig. 3.

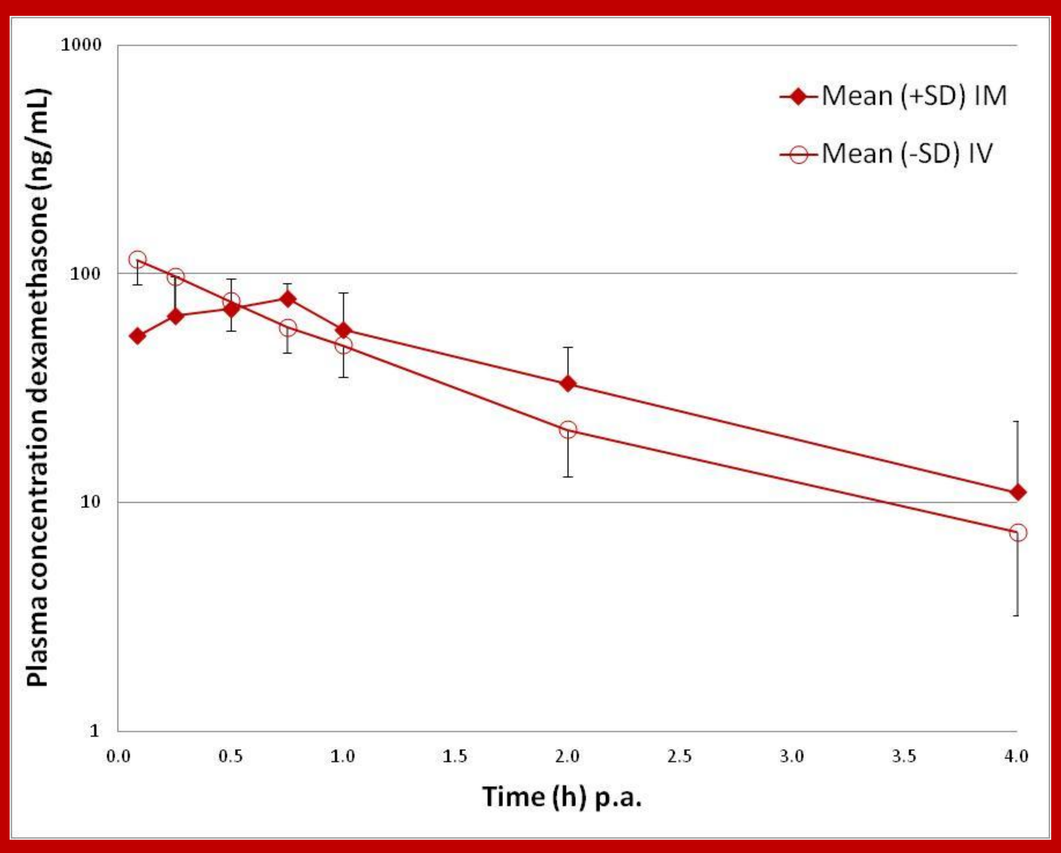


Figure 3. Mean (± SD) plasma concentration-time profiles of dexamethasone after IV and IM bolus administration of 0.3 mg/kg BW in pigs (n=6)

Table 1. Pharmacokinetic parameters for dexamethasone in pigs after IV and IM bolus administration of 0.3 mg/kg BW (n=6, mean ± SD)

| Parameter | Units | IV | IM |
|---|---|---|---|
| $AUC_{0\rightarrow\infty}$ | h.ng/mL | 133.07 ± 39.59 | 173.24 ± 53.59 |
| $k_{abs}$ | /h | - | 12.90 ± 10.57 |
| $k_{el}$ | /h | 0.90 ± 0.28 | 0.65 ± 0.30 |
| $T_{1/2abs}$ | h | - | 0.05[A] |
| $T_{1/2el}$ | h | 0.77[A] | 1.06[A] |
| $V_d$ | L/kg | 2.78 ± 0.88 | 3.04 ± 0.71 |
| Cl | L/h.kg | 2.39 ± 0.57 | 1.88 ± 0.60 |
| $T_{max}$ | h | - | 0.35 ± 0.21 |
| $C_0$ | ng/mL | 114.89 ± 26.56 | - |
| $C_{max}$ | ng/mL | - | 80.94 ± 21.29 |
| F | % | - | 131.06 ± 26.05 |

[A]:harmonic mean

## Materials and Methods

### Experimental protocol

The experiment was performed as a two-way cross-over design with each group containing three 9-week-old male pigs. A wash-out period of 5 days was taken into account. The animals received a bolus of 0.3 mg/kg body weight DEX-sodium phosphate (DEXA 0.2%®, Kela Laboratories, see Fig. 1B) intravenously (IV) in the ear vein or intramuscularly (IM) in the *m. gluteus*. Blood was collected from the jugular vein before (time 0) and post-administration (0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12 and 24 hours). Plasma was stored at ≤ -15°C until analysis.

### DEX analysis

Quantitation of the active form of DEX (Fig. 1A) in plasma was carried out using an in-house developed and validated liquid chromatography-tandem mass spectometry (LC-MS/MS) method. This is shown in Fig 2.

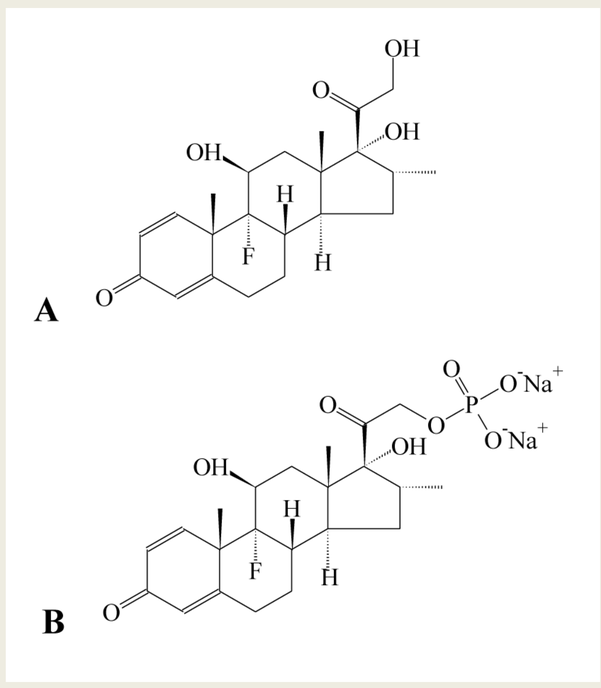


Figure 1. Chemical structures of DEX (A) and the ester prodrug, DEX-sodium phosphate (B)

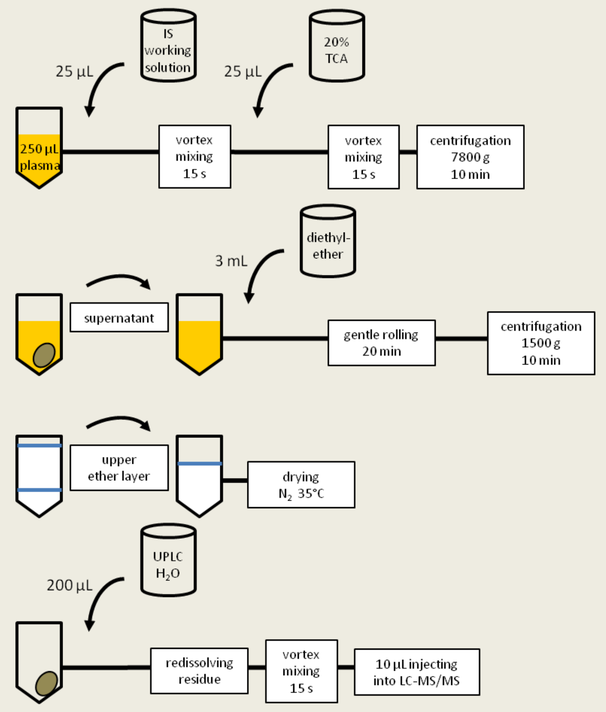


Figure 2. Diagram of DEX analysis using a LC-MS/MS method

### PK and Statistical analysis

The PK parameters were analyzed using WinNonlin, version 6.2.0 (Pharsight). A one-compartmental model was used to determine the $AUC_{0\rightarrow\infty}$, $k_{abs}$, $k_{el}$, $T_{1/2abs}$ and $T_{1/2el}$ (expressed as the harmonic mean), $V_d$, Cl, $C_0$, $C_{max}$ and $T_{max}$.
The absolute bioavailability (F) was calculated from the following equation:

$$F\ (\%) = (AUC_{0\rightarrow\infty\ IM} / AUC_{0\rightarrow\infty\ IV}) \times 100$$

The data were statistically analysed by means of single-factor analysis of variance (ANOVA), using PASW Statistics 18 (IBM SPSS Software). A value of $P<0.05$ was considered significant.

## Discussion and Conclusion

In pigs, a remarkably high clearance of DEX is observed, which is noticeably faster than in other mammalian species. It also resulted in a rather short half-life of elimination, notwithstanding the rather high volume of distribution.
None of the pharmacokinetic parameters were significantly different between both administration routes.

**We can conclude that there is a complete and fast absorption as well as a fast elimination of the active substance of DEX-sodium phosphate following IM administration in pigs.**

In future research, these pharmacokinetics will be applied in a porcine LPS-inflammation model to investigate the individual and synergistic immunomodulatory properties of DEX.
The influence of DEX on the pro-inflammatory cytokines, acute phase proteins and fever suppression will be investigated.

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